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Dalbavancin: A New Pathway for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Portugal

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Abstract

Background: Acute bacterial skin and skin structure infections are frequent in-hospital infections. Vancomycin and linezolid are antibacterial agents commonly used in serious acute bacterial skin and skin structure infections but have been associated to prolonged length of stay. Dalbavancin is a new lipoglycopeptide antibacterial, active against Gram positive pathogens, with a long half-life, allowing for a single infusion of 1500 mg or 1000 mg followed one week later by 500 mg. The aim of this study was to assess the effect of dalbavancin on length of stay and mortality of acute bacterial skin and skin structure infections patients in Portugal.

Methods and findings: we have modelled the natural history and treatment implications of acute bacterial skin and skin structure infections using a decision analytical tree that calculated the probability of success, failure or death for dalbavancin and linezolid. Efficacy endpoints were obtained from a randomized controlled trial. LOS and mortality due to acute bacterial skin and skin structure infections were derived from non-experimental studies.

Conclusion: we estimated the average length of stay for dalbavancin in 10.4 days. Compared to linezolid this represents a 9.4 day reduction. Dalbavancin is estimated to decrease the death rate by 1.7% in serious acute bacterial skin and skin structure infections caused by Gram positive pathogens and by 1.8% in acute bacterial skin and skin structure infections caused by methicillin-resistant *Staphylococus aureus*.

Keywords: Acute bacterial skin and skin structure infections; Methicillin-resistant *Staphylococcus aureus*; Dalbavancin; Linezolid

Abbreviations: ABSSSI: Acute Bacterial Skin and Skin Structure Infections; LOS: Length of Stay; MRSA: Methicillin-resistant *Staphylococcus aureus.*

Introduction

Acute bacterial skin and skin structure infections (ABSSSI) are the 4th most frequent cause of in hospital infections in Portugal, accounting for 10.1% of all cases; *Staphylococcus aureus* and streptococci species are the most prevalent causing agents [1,2]. In Portugal, methicillin-resistant *Staphylococcus aureus* (MRSA) represents 46.8% of all *Staphylococcus aureus* species isolates [2]. Retrospective observational data from 12 European countries identified an average length of stay (LOS) in Portuguese hospitals of 25 days for ABSSSI patients, with vancomycin and linezolid as the most used antibacterial agents [3]. Current antibacterial agents used for ABSSSI have limitations concerning safety [4,5] development of resistant strains [6] and patients' suboptimal adherence to complex regimens [7-9]. ABSSSI are therefore considered a major driver for resource utilization in Portuguese hospitals. Dalbavancin is a new lipoglycopeptide antibacterial agent that is active against Gram positive pathogens. Its extended half-life (8.5 days) and safety profile allow a simplified regimen (either a single infusion of 1500 mg or 1000 mg followed one week later by 500 mg), enhanced compliance and, potentially, early discharges. In selected cases, dalbavancin may be administered in an outpatient setting, which may be of additional benefit when compared to antibacterial agents requiring daily inpatient administration [10,11].

In randomized controlled clinical trials, dalbavancin was non-inferior to linezolid with eradication proportions of Gram positive pathogens of 89.5% *vs.* 87.5%. In the sub-population of ABSSSI caused by MRSA the eradication proportions were 91% and 89% for dalbavancin and linezolid respectively [12]. The objective of this study was to assess the impact of dalbavancin in LOS and mortality due to ABSSSI in Portugal.

Material and Methods

We have modelled the natural history of ABSSSI and its treatment implications using a decision analytical tree. Decision analytical trees are largely used in health and medicine modelling as a method of supporting analysis and decision making [13,14]. Our tree had an initial node related to first line treatment option with three mutually exclusive possible outcomes: success, failure or death. In case of first line treatment failure, patients started a second line treatment. Because of the high cure rates observed in clinical trials and incorporated within the model, the probability of therapy failure in the second line of treatment would be marginal (less than 1%). Therefore, the node for second line treatment considered only success or death as outcomes (Figure 1), i.e., no third line treatments have been considered.

Assumptions

The model was based on the following assumptions: (I) linezolid as comparator for dalbavancin as first line treatment and vancomycin as second line treatment for both; this choice was made based on linezolid superiority against vancomycin in clinical outcomes, skin complications and length of hospital stay, as reported by systematic

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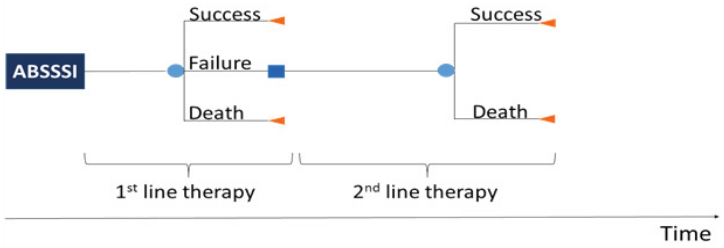

Figure 1: Decision tree model adopted for Acute Bacterial Skin and Skin Structure Infections.

reviews [15]; (II) efficacy endpoint, defined as microbiological efficacy, 14 days after treatment completion, as reported in the randomized clinical trial [12]; (III) safety endpoints, defined as the occurrence of any adverse event with a ≥ 3% frequency for both arms, as reported in randomized clinical trials [12,16]; (IV) assessment of results in the overall population with a baseline Gram positive pathogen and a separate analysis for the population infected with MRSA; the eradication of Gram positive pathogen 14 days after treatment completion results was used as probability of success, based on the treatment duration recommended in current guidelines [17]; (V) due to the acute nature of the disease and high cure rates, second line therapy patients have only two possible outcomes: success or death; (VI) time horizon comprehending the in-hospital stay and the outpatient care periods, including second-line therapy.

ABSSSI probability of death was calculated at 3.8%, the weighted average of ABSSSI in-patients hospital death retrieved from non-experimental studies [18-21].

We have calculated failure to first line therapy applying the reported microbiological failure rates [12] (dalbavancin: 1-0.89 in the overall population and 1-0.91 in the MRSA population; linezolid: 1-0.875 in the overall population and 1-0.89 in the MRSA population) to the survival probability (inserted in the model as [1 - probability of death, P_{death}]).

In order to identify the percent reduction obtained in mortality (%RM) with dalbavancin *versus* linezolid for the population with a Gram positive pathogen, the following formula was used:

% RM(a) = 1 – [Pdeath (first line) + Pdeath after drug failure]/ [Pdeath (first line) + Pdeath after comparator failure]

The same rationale was used for the MRSA population; in this case the proportion of patients with MRSA in the population with a Gram positive pathogen (51.17%) was also incorporated

% RM(b) = 1 – (P_{MRSA} (Gram +) x [P_{death} (first line) + P_{death} after drug failure] / P_{MRSA} (Gram +) x [P_{death} (first line) + P_{death} after comparator failure]

Since dalbavancin is a recent antibacterial agent, there are no published reports concerning its real world LOS in ABSSSI patients. The ratio between linezolid's 19.8 days LOS and its 15.2 days duration of treatment (Angelini/Vicuron data on file-VER001-9 Clinical Study report 2014] is, approximately, 1.3. To compare the LOS associated to the two antibacterial agents the same ratio was applied as a correction factor to dalbavancin duration of treatment-assumed, in the model, as the total number of days from the first to the second infusion (8 days). The model was computed using Microsoft Excel 2013 software.

Results

Dalbavancin is estimated to additionally decrease the in-hospital death rate by 1.7% (standard deviation (SD): 2.7%) in the population with an identified Gram positive pathogen and by 1.8% (SD: 3.9%) in MRSA infected sub-population when compared to linezolid (Figure 2).

The average LOS with dalbavancin was estimated to be 10.4 days [22]. Compared to the average LOS (19.8 days) for linezolid, this represents an average reduction of 9.4 days in the hospital LOS for ABSSSI patients (Figure 3).

Discussion

Treatment of ABSSSI with dalbavancin is estimated to reduce LOS in 9.4 days (47%) *versus* linezolid, which is one of the current gold-standard antibacterial agents in use for the treatment of these infections. In-hospital death rate is expected to be reduced with dalbavancin by 1.7% and 1.8%, in the population infected by a Gram positive pathogen and by MRSA, respectively, when compared to linezolid. MRSA infected patients are estimated to benefit from a higher impact in in-hospital death rate when compared to the population infected by a Gram positive pathogen, which is a relevant potential outcome.

These results reflect the therapeutic value of dalbavancin in the treatment of ABSSSI, which is mainly driven by its convenient administration schedule and high efficacy in MRSA infected population [12]. The current model was the first to estimate LOS and in-hospital mortality in ABSSSI, in Portugal.

Some limitations have to be considered when interpreting these findings, particularly due to the characteristics of the developed model; as with any model, they should be validated in a real-world context.

The model did not incorporate a separate analysis for vancomycin intermediate resistant *Staphylococcus aureus* (VISA) patients where dalbavacin's efficacy is expected to be higher. Patients' adherence was not incorporated in the model. As dalbavancin is an IV regimen with two or one single administration, therapy adherence is expected to be superior to a twice daily regimen such as linezolid's, which could contribute to more favorable outcomes for dalbavancin.

This model does not capture the potential health risks associated with a prolonged LOS that can additionally affect the burden of ABSSSI. In fact, the benefits of achieving reductions in LOS go far beyond financial savings. The longer the patient stays in a hospital setting the higher the probability of hazardous in-hospital occurrences, such as hospital acquired infections [23]. LOS has also been identified as a mediator of hospital-acquired MRSA [24]. As the European Medicines Agency currently identifies the development of drug resistance as one of the risks of antibacterial agents usage to be addressed through risk management plans [25], the choice of antibacterial agents could potentially be optimized when the associated LOS is taken into account

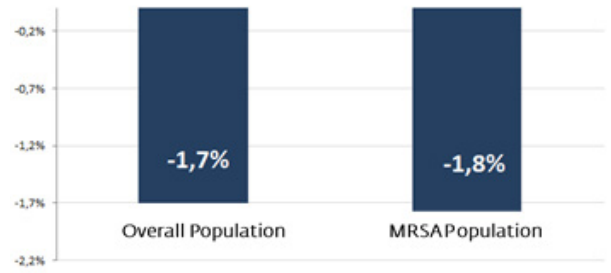

Figure 2: Estimated decrease in death rate achieved with dalbavancin *versus* linezolid as first line treatment (and vancomycin as second line treatment for both cases) in the populations with ABSSSI due to a Gram positive pathogen and MRSA.

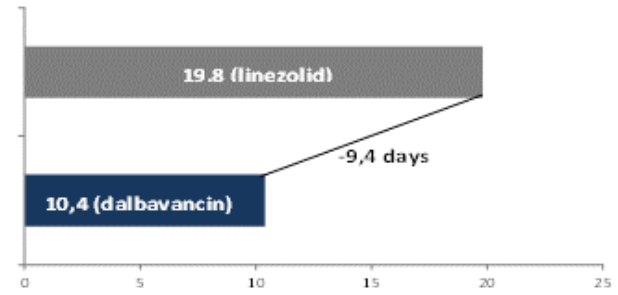

Figure 3: Average length of stay estimated for the treatment of ABSSSI with dalbavancin or linezolid as first line (and vancomycin as second line treatment in both cases).

[17]. Reductions in hospitalization length are officially recommended in guidelines concerning the management of ABSSSI [17]. An early discharge may represent additional emotional gains to patients (e.g., relatives proximity, privacy, familiar environment); outpatient parenteral antibacterial therapy programs, when possible, have been associated to high levels of patient satisfaction [26]. We have not included these aspects in our analysis.

These unexploited areas could add to the benefits described above and are suggested to be the object of future research in the field of ABSSSI antibacterial treatment.

Conclusion

Dalbavancin is an effective new approach to provide intravenous antibiotic therapy for patients with ABSSSI, with a favorable safety profile and a simplified dose regimen. Its use as an in-hospital first line intravenous antibiotic therapy to treat severe ABSSSI has the potential to decrease LOS and ABSSSI-associated mortality when compared to first line use of linezolid.

Competing and Conflicting Interests

Helena Sofia Antão and João Paulo Guimarães work in the medical department of Angelini. João Almeida and Susana Marques work for Exigo, a scientific consulting company contracted for the execution of the model.

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